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Familial Translocation t(Y;15)(q12;p11) and De Novo Deletion of the Prader-Willi Syndrome (PWS) Critical Region on 15q11-q13

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We describe a 17-year-old girl with mild Prader-Willi syndrome (PWS) due to 15q11-q13 deletion. The deletion occurred on a paternal chromosome 15 already involved in a translocation, t(Y;15)(q12;p11), the latter being present in five other, phenotypically normal individuals in three generations. This appears to be the first case of PWS in which the causative 15q11-q13 deletion occurred on a chromosome involved in a familial translocation, but with breakpoints considerably distal to those of the familial rearrangement. The translocation could predispose to additional rearrangements occurring during meiosis and/or mitosis or, alternatively, the association of two cytogenetic anomalies on the same chromosome could be fortuitous. Am. J. Med. Genet. 70: 222–228, 1997. © 1997 Wiley-Liss, Inc.

KEY WORDS: Prader-Willi syndrome; chromosome 15; Y chromosome; translocation; microdeletion

INTRODUCTION

Prader-Willi syndrome (PWS) [Prader et al., 1956] is characterized by congenital hypotonia (94%), obesity of early childhood onset (94%), mental deficiency (97%), short stature (76%), small hands and feet (83%) hypogenitalism/hypogonadism (95%), and a characteristic face [Butler, 1990; Donaldson et al., 1994; Butler et al., 1995; Webb et al., 1995]. The incidence of PWS is estimated at about 1 in 25,000 live births [Zellweger and Soper, 1979].

Most cases of PWS occur sporadically. In 70–80% of patients there is a deletion of the region 15q11-q13 on the paternally-derived chromosome, whereas maternal uniparental disomy (UPD) is present in about 20% of cases [Ledbetter et al., 1981; Butler et al., 1986; Nicholls et al., 1989; Robinson et al., 1991, 1993a,b; Mascari et al., 1992]. A small number of patients have neither deletion nor UPD; in some of these, mutations in a hypothetical gene(s) controlling imprinting of the 15q11-q13 region may be responsible for PWS [Glenn et al., 1993; Lerer et al., 1994; Reis et al., 1994; Webb et al., 1994, 1995; Woodage et al., 1994].

Some PWS patients have unbalanced translocations involving chromosome 15 with deletion of the PWS region from the paternal chromosome [Rivera et al., 1990; Butler, 1990] or balanced Robertsonian translocations with proven [Nicholls et al., 1989; Smith et al., 1993] or presumed maternal UPD [Berry et al., 1981; Casamassima et al., 1991; Smith and Noël, 1980].

We report here the association of PWS with a familial translocation involving chromosomes Y and 15, t(Y;15)(q12;p11).

Although several de novo Y;15 translocations have been described previously in PWS patients [Berry et al., 1981; Kousseff et al., 1987; Qumisiyeh 1992; Vickers et al., 1994], the translocation breakpoints were always within the PWS critical region. The patient described here had both a familial translocation affecting the short arm of chromosome 15 (outside the PWS critical region) and a de novo 15q11-q13 deletion on the translocated chromosome. The familial translocation may have predisposed to the generation of microdeletion within the PWS region on chromosome 15, or the association may be fortuitous.

FAMILY AND METHODS

Proposita (III-2)

The proposita, a 17-year-old girl, was referred to the pediatric endocrinology clinic for primary amenorrhea and short stature. She was the first child of healthy non-consanguineous parents of Sicilian origin (Fig. 1). The mother was 26 and the father 27 years old at the time of her birth. Both were 162 cm tall. Spontaneous delivery occurred at 36 weeks after an uneventful preg-

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nancy; birth weight was 2.1 kg (10th centile), length was 44 cm (10th centile), and head circumference (OFC) was 33.5 cm (75th centile). Bottle-feeding with enlarged-pore nipples was required because of neonatal hypotonia. Before the age of 2 years she began to gain weight and was moderately obese by age 2 1/2 years. Mild psychomotor delay was observed; two elementary school grades were repeated. She was referred to the genetics clinic by the pediatric endocrinologist at age 17, at which time she weighed 53.7 kg (+ 4 SD for height) and measured 145.5 cm (<3rd centile); OFC was 53.5 cm (25th centile). Hands and feet were small (10th centile). Bone age was 15 years. She had postpubertal sexual characteristics: breast development B5, pubic hair PP4, and axillary hair A3, according to modified Tanner stages [Sizonenko et al., 1970]; vulva was of adult type. Hormonal plasma levels were in the normal pubertal range for FSH and LH (8.2 and 5.4 mU/ml, respectively), with a normal pubertal response to gonadotropin-releasing hormone (50 mg I.V.), LH response (16.0 mU/ml) being higher than FSH (111.4 mU/ml). Plasma estradiol was low (16.1 pg/ml). During a night study, the normal pulsatility of FSH and LH was not observed, and growth hormone (GH) levels were low, probably in relation to obesity. Growth hormone response to GH-releasing hormone (15.6 ng/ml) was at the lower limit of the normal. Plasma IGF1 (203 ng/ml) and IGFBP3 (4.7 mg/l) were normal for age. Basal plasma levels of prolactin were slightly elevated (17.2 ng/ml), and the response to TRH was normal. It was concluded that primary amenorrhoea was due to isolated hypogonadotropic hypogonadism. No anosmia was detected. Cyclic therapy with estradiol valerate and norgestrel (Cyclacur(R), 21 days/month) was instituted, resulting in normal menstruation. Discontinuation of the therapy during 4 months was accompanied by amenorrhoea, confirming the hypogonadotropic hypogonadism. Cyclic therapy was reinstituted for 1 year.

On a PWS diagnostic scale [Holm et al., 1993] she scored 8.5 points (at least 8 points, of a total of 13.5, are considered necessary for a diagnosis). The clinical diagnosis of PWS was made, although her phenotypic features were mild.

Her parents and brother, paternal aunts, and an uncle (Fig. 1) were phenotypically normal.

Cytogenetic Analysis

Chromosome spreads at a 550 band resolution level were obtained after culture and harvest of PHA-stimulated lymphocytes. GTG and CBG banding and AgNOR staining were performed by standard procedures [Verma and Babu, 1989].

Molecular Analyses

The methylation status of the PWS region was assessed by Southern blotting, following digestion with HpaII and HindIII of genomic DNA from all living relatives. The probe used was pPW71 (D15S63) [Dittrich et al., 1992].

The extent of the microdeletion in the proposita and the inheritance of specific chromosome 15 loci were determined by PCR analysis of microsatellite polymorphisms and Southern blotting. The microsatellites used were D15S541, D15S542, D153543, D15S10, GABRB3, GABRA5, D15S156, D15S219, D15S165, and ACTC (primer sequences and information on these loci are available in Genome Database, http://gdbwww.gdb.org). Quantitative Southern blotting was performed with D15S12 (pIR10-1), after digestion of genomic DNA with ScaI.

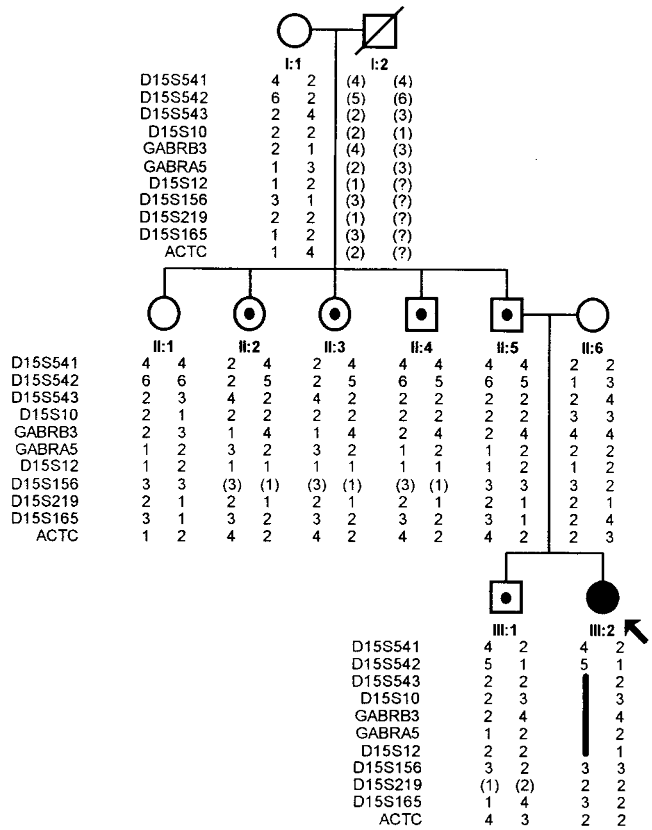

Fig. 1. Pedigree and genotypes of the proposita's family. Asymptomatic carriers of the translocation are depicted by symbols containing a solid dot. The chromosome 15 polymorphic markers are arranged from centromeric (top) to telomeric (bottom); alleles for which the phase could not be determined are in parentheses. The extent of the deletion in the proposita (III-2) is represented by a solid bar.

Two-colour fluorescent in situ hybridization (FISH) was performed on metaphase spreads from the peripheral blood lymphocytes. The translocation was characterized by simultaneous hybridization with the Y chromosome-specific probe DYZ1 (kindly provided by Dr. H. J. Cooke, Edinburgh) and the chromosome 15 centromeric probe D15Z4. The deletion was characterized by hybridization with P1 probes for D15S113 (in the region commonly deleted in PWS) and a distal control probe for PML (15q23-q25) (both probes kindly supplied by Dr. J. Gray, Lawrence Berkeley National Laboratory, UCSF). Hybridization was performed as described [Karayiorgou et al., 1995] and images captured and analysed with a Cytovision Probe workstation (Applied Imaging).

RESULTS

Cytogenetics

The proposita's karyotype was 46,XX,15ps+ (Fig. 2). By CBG-banding the short arm of this der(15) was shown to be mainly heterochromatic, suggesting a Y chromosome origin. There was no AgNOR staining of the der(15). Thus the karyotype was interpreted as 46,XX,der(15)(15qter → 15p11::Yq12 → Yqter). No cytogenetically-detectable deletion in the Prader-Willi critical region was present.

The father's karyotype was 46,XY,der(15) t(Y;15)(q12;p11) and the mother's normal, 46,XX. An apparently identical der(15) was observed in the proposita's brother and in three of four of the father's sibs (II-2 to II-5 and III-1). It was not present in the paternal grandmother; the grandfather was deceased and no samples were available for study.

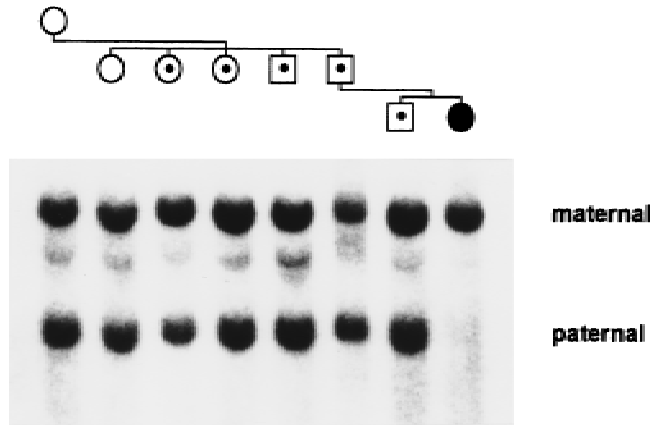

Fig. 3. Southern blot analysis of the methylation status of the locus D15S63. Genomic DNA was restricted with HindIII and HpaII, and the blot hybridized with the probe PW71. The absence of a paternally-derived band in the proposita is typical of Prader-Willi syndrome.

DNA Studies

Methylation status of the PWS region. The family was analysed by Southern blotting at the locus D15S63, following double-digestion of the DNA with HindIII and HpaII to determine the methylation status of the PWS region. The proposita (III-2) had an abnormal methylation pattern, with absence of a paternally-derived band (Fig. 3) [Dittrich et al., 1992].This result is typical of Prader-Willi syndrome and thus confirms the clinical diagnosis of PWS in the proposita. All other relatives, including the five carriers of the translocation (II-2 to II-5, III-1) had normal patterns.

Microsatellite and Southern blot analysis of chromosome 15 loci. Genotypes of ten microsatellite polymorphisms were determined in all relatives. The markers used and their relative mapping positions are shown in Figure 4A; results from selected markers are shown in Figure 4B. D15S10 revealed a microdeletion in chromosome 15q11-q13 in the proposita, with clear absence of a paternal allele. In addition, the relative band intensities of marker D15S543 (the PCR amplification for which simultaneously detects a single-copy chromosome 16 polymorphic locus) suggested that this locus too was deleted.

The proximal end of the deletion was localized within an interval of 2.7 cM between markers D15S541/542 (non-deleted) and D15S543 (deleted). This is equivalent to the proximal breakpoint of type II PWS/AS deletions [Christian et al., 1995].

The distal end of the deletion was defined by microsatellite and Southern blot analysis. Marker D15S165 showed two alleles in the proposita, whereas hybridization with D15S12 indicated that the proposita was hemizygous for this locus. The deletion therefore extends throughout the common PWS/AS deletion region [Christian et al., 1995].

Genotyping of additional polymorphic markers from D15S543 to D15S219 showed only one allele per locus in the proband. This is compatible with, but not necessarily indicative of, deletion at these loci, since the genotypes of the parents were not fully informative (Figs. 1, 4).

Microsatellite analysis of the other family members confirmed that none of the other five translocation carriers had detectable deletions in the PWS/AS region.

Fluorescent in situ hybridization (FISH). Metaphase spreads from the proposita (III-2) and her father (II-5) were hybridized with probes for the Y chromosome (DYZ1) and for the chromosome 15 centromere (D15Z4) (Fig. 5). The t(Y;15) chromosome in the father clearly contains the chromosome 15 centromere, indi-

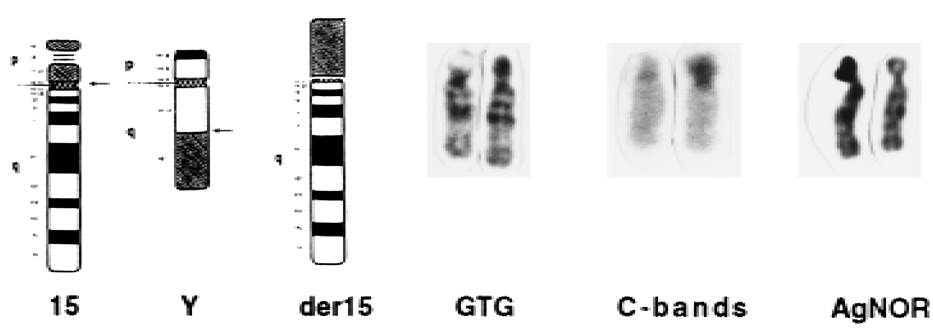

Fig. 2. Cytogenetic characterization of the t(Y;15) translocation. **Left:** Idiograms of normal chromosomes 15 and Y and the derivative chromosome (the breakpoints are marked by small arrows). **Right:** The normal (left) and derivative (right) chromosome 15 in the proposita.

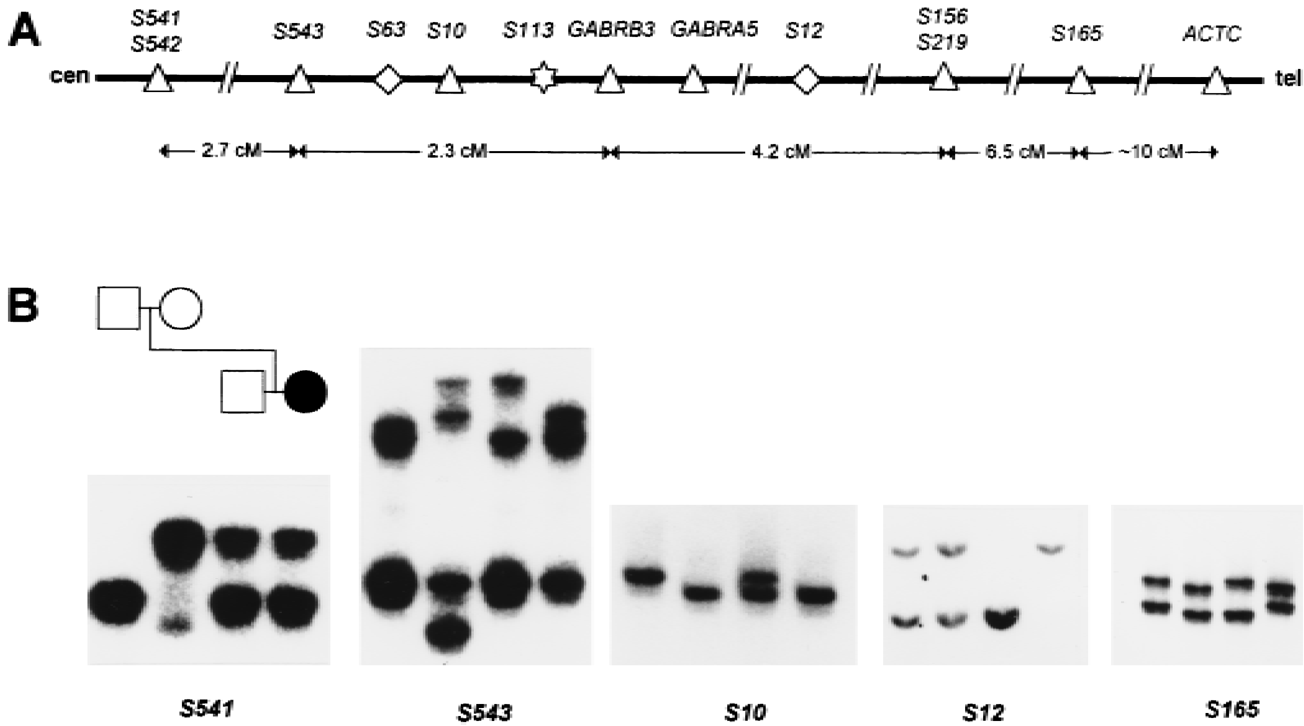

Fig. 4. Genetic analysis of the 15q11-q13 region in the proposita and her immediate family. **A:** Schematic map of the markers used. The deletion in the proposita extends from D15S543 to D15S12 (inclusive). Triangles represent microsatellite-based polymorphic loci, diamonds represent loci analyzed by Southern blotting, and star represents the marker analyzed by FISH. **B:** Selected informative markers, presented in the order father-mother-healthy brother-proposita. D15S543, D15S10, and D15S12 are deleted in the proposita, D15S541 and D15S165 are undeleted. The D15S543 primers detect two loci; the lower bands represent the chromosome-15-specific locus.

cating that the original translocation breakpoint on chromosome 15 was in the short arm, far removed from the PWS/AS region. No structural alteration was detected in the proposita using these two probes.

In contrast, hybridization of the proposita's DNA with a D15S113 probe demonstrated a de novo deletion within the PWS/AS region (Fig. 5), confirming the results of the DNA analysis.

DISCUSSION

We describe here a family with an inherited translocation t(Y;15) in which the chromosome 15 breakpoint was located on the short arm of chromosome 15, far removed from the PWS region; five individuals carrying this translocation had normal phenotypes. A sixth member of this family, affected with Prader-Willi syndrome, showed a de novo deletion of the PWS region on the paternally-derived t(Y;15) chromosome. The proximal breakpoint was equivalent to that of molecularly-defined type II deletions [Christian et al., 1995] and the deletion extends throughout the usual PWS/AS region, i.e., beyond marker D15S12.

It has been proposed that deletions of the PWS/AS region may be mediated by low-copy repeat sequences which predispose to abnormal pairing and unequal crossing-over, thus resulting in deletion or duplication events [Christian et al., 1995]. Buiting et al. [1995] described a multi-locus gene family on chromosome 15 which could contribute to the instability of the 15q11-q13 region. Other situations in which submicroscopic deletions or duplications have been associated with flanking repeats include deletions of the STS gene at Xp22.3, resulting in X-linked ichthyosis, duplications of 17p11.2-p12 in Charcot-Marie Tooth type 1A, and deletions of the same region in hereditary neuropathy with liability to pressure palsies [Ballabio et al., 1990; Pentao et al., 1992; Chance et al., 1994].

The genotypes of DNA polymorphisms flanking the de novo deletion of the PWS/AS region in individual III-3 suggest that there was no crossing-over associated with the deletion. The phase of the markers was identical in the paternal and the proposita's t(Y;15) chromosomes, rendering unlikely a deletion mechanism via mispairing and unequal crossing-over in this case (unless there were two cross-over events between the flanking markers). In contrast, a deletion resulting from a DNA loop-out, maintaining the order of the parental markers, is compatible with our data. The hypothesis that this region is particularly unstable and subject to meiotic and perhaps mitotic rearrangement is also supported by the observation of several cases of Prader-Willi and Angelman syndromes associated with supplementary inv dup(15) chromosomes [Robinson et al., 1993a,b]. Alternatively, the association of these two cytogenetic anomalies on the same chromosome could be fortuitous.

The deletion of the paternal PWS/AS region in the patient described here could have occurred during meiosis or mitosis. A mitotic event can often be de-

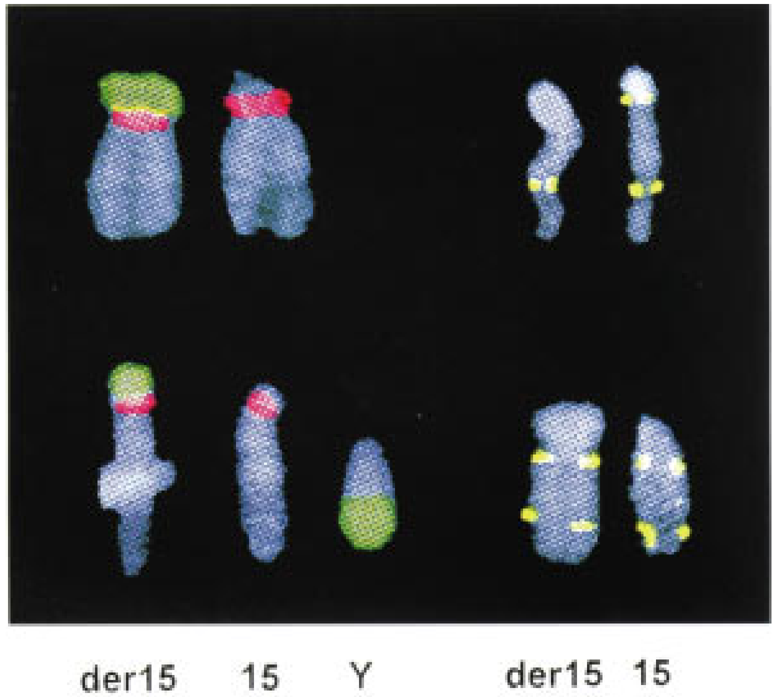

Fig. 5. Characterization by fluorescent in situ hybridization (FISH) of the t(Y;15) translocation, in the proposita (upper) and the father (lower). Red, chromosome 15 centromere (D15Z4). Green, Y chromosome heterochromatin (DYZ1). Yellow, D15S113 and PML (control probe).

tected as such by molecular analysis since it creates mosaicism of two cell populations with different DNA profiles. Indeed, a mitotic origin of the error leading to mosaicism would be compatible with the relatively mild PWS phenotype in the proposita. No evidence for such mosaicism, i.e., a cell population with the t(Y;15) but without the deletion, was detected by our DNA polymorphism analysis, methylation and FISH studies in the proposita. However, a non-deleted cell population of less than 5% would go undetected by the methods described here [Pangalos et al., 1994].

Do translocations involving chromosome 15 predispose to further aberrations of the PWS/AS region of chromosome 15? Few such cases have been reported. Smith and Noël [1980] described a Robertsonian translocation t(14;15) in a mother and three of her seven children. One of the offspring with the t(14;15) had Prader-Willi syndrome. A similar case was reported by Berry et al. [1981], in which a phenotypically-normal mother with a Robertsonian t(13;15) transmitted the abnormal chromosome to her daughter, who was diagnosed with PWS. However, since no DNA analysis was performed in these two cases it is unknown whether the PWS was a consequence of maternal UPD(15) or deletion of the paternal allele in the PWS/AS region.

Casamassima et al. [1991] described a mother and three sons with a Robertsonian t(13;15); one son with PWS showed, on high resolution chromosomal analysis, a del(15)(q11.2-q13) on the chromosome 15 not involved in the translocation. Smeets et al. [1992] described a three-generation family with a balanced t(6;15)(p25.3;q11.1). Two first cousins had inherited the familial translocation from their fathers. In one individual with Angelman syndrome, DNA analysis showed paternal UPD(15). The other cousin, with PWS, showed a deletion in the PWS/AS region on the translocated chromosome 15. Clayton-Smith et al. [1993] reported on a family in which two first cousins, one with AS and the other with PWS, had cytogenetically-visible deletions of the PWS/AS region on the chromosome 15 involved in a familial rearrangement, inv(15)(q11.2;q15).

In several of the families described above, in which DNA analysis was performed, a de novo paternally derived deletion of the PWS/AS region was observed in the context of a familial rearrangement involving chromosome 15. In contrast to the patient described here, all the other translocation breakpoints involved the 15q11-q13 region.

There is precedent for the association of a familial translocation with a deletion elsewhere on the same chromosome, if Robertsonian translocations involving other chromosomes are considered: for example, Bonthron et al. [1993] described a dysmorphic and retarded female with an interstitial deletion 14q32 and a paternally-derived Robertsonian translocation t(14;21).

There is also ample precedent for the association of abnormal phenotypes with apparently balanced familial translocations, Robertsonian or reciprocal [Fryns et al., 1991; Wenger et al., 1995]. Mechanisms for the production of such phenotypic abnormalities include cryptic translocations [Wagstaff and Hemann, 1995], submicroscopic deletions or duplications due to unequal crossing-over, uniparental disomy of one of the chro-

mosomes involved [Engel and DeLozier-Blanchet, 1991], and disruption of imprinting [Weksberg et al., 1993].

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